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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,070	03/03/2006	Sutisak Kitareewan	DC0266US.NP	5026

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LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1653	

NOTIFICATION DATE	DELIVERY MODE
06/15/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOactions@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)
	10/564,070	KITAREEWAN ET AL.
	Examiner	Art Unit
	PAUL MARTIN	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Claim 8 is pending in this application and was examined on its merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 is newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Bard *et al.*(1977) in view of Yoshida *et al.* (1996) as evidenced by Adamson (1996).

Bard *et al.* teaches that at higher than physiological concentrations the known anticancer retinoid compounds at 2, 5, 10 and 20 μM destabilize membranes causing the release of lysosomal enzymes and that the effect can be followed by metachromatic staining and by measuring the appearance of proteoglycan fragments in the medium of organ cultures of rabbit ear cartilage (Pg. 115, Column 1, Lines 25-36 and Column 2, Lines 1-3 and 14-25).

Bard *et al.* does not teach a method comprising contacting a cell expressing PML/RARα and detecting whether said agent destabilizes lysosomes of the cell as determined by vital staining of lysosomes or release of lysosomal proteins into the cytosol; and increases lysosomal-dependent PML-RARα protein degradation.

Yoshida *et al.* teaches a method of identifying an agent that increases oncogenic protein degradation comprising contacting an APL (acute promyelocytic leukemia) cell that expresses PML/RARα with the anti-cancer agent ATRA *(all-trans-retinoic* acid) at concentrations of 1, 0.1 and 0.01μM (Pg. 2945, column 1, Lines 29-31) and detecting whether ATRA increases PML/RARα protein degradation (Pg. 2946, Column 2, Lines 22-29 and Pg. 2947, Column 1, Lines 1-5 and Fig. 4).

Adamson teaches the use of all-*trans*-retinoic acid (ATRA) as a potent remission agent in the treatment of acute promyelocytic leukemia (APL) and wherein following a typical oral dose of 45mg/m^2 of ATRA, peak plasma concentrations on the first day of treatment range from 0.1 to 8 μM with a media peak of 1 μM (Pg. 305, Abstract and Pg. 307, column 2, Lines 33-38).

It is inherent in the methods of Yoshida *et al.* and Bard *et al.* that a dose of 1, 2 and 5 μM would constitute an effective amount of ATRA as it falls within the clinically useful concentrations (0.1-8 μM) as evidenced by Adamson.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the teachings of Bard *et al.* whom teaches that retinoid compounds destabilize membranes causing the release of lysosomal enzymes and that the effect can be followed by metachromatic staining and by measuring the appearance of proteoglycan fragments in the medium of organ cultures of rabbit ear cartilage to use cells expressing PML-RARα because the method of Bard *et al.* is not limited to any particular cell type and thus it would have been obvious to one of ordinary skill in the art that any cell type could be exposed to retinoids and monitored for lysosomal destabilization. Those of ordinary skill in the art would have also been aware that as lysosomes destabilize, they release lysosomal enzymes into the cytosol which would actively degrade any proteins they encounter, including the protein PML-RARα, if present. Therefore, the combined method of Bard *et al.* and Yoshida *et al.* would serve to identify an agent (retinoic acid) causing the destabilization of lysosomes in cells expressing PML-RARα and inherently increasing lysomal-dependent PML-RARα protein degradation (in addition to many other proteins). The limitation that the protein degradation be "lysosomal dependent" is inherently met as the destabilization of the lysosomes releases enzymes and would not otherwise occur, making the resulting protein degradation necessarily "lysosomal dependent".

Response to Arguments

Applicant's arguments filed 05/12/2011 have been fully considered but they are not persuasive.

The Applicant argues that the amendment to Claim 8 to recite that the method involves contacting a cell that expresses PML/RARα with an "effective amount" of an agent as well as stating that "an effective amount of said agent is a concentration that is clinically useful", i.e., "one that is in an amount sufficient to effect beneficial or desired results, including clinical results" is sufficient to non-obviate the rejection as Bard *et al.* teaches retinoids at concentrations of 2 to 20 μm, allegedly doses which are not clinically useful due to undesired toxicity involving lysosomal destabilization, an attribute allegedly not sought when developing or screening drugs for anti-cancer properties. Applicant suggests this as a "teaching away" from the instant method which relies on the ability of an agent to destabilize lysosomes within a cell as a desired drug effect (Remarks, Pg. 4, Lines 7-31 and Pg. 5, Lines 1-34 and Pg. 6, Lines 1-10).

This is not found to be persuasive for the following reasons, as discussed above, both Bard *et al.* and Yoshida *et al.* teach the use of ATRA in "effective amounts" as broadly defined in the instant Specification at Pg. 15, Lines 13-23 as: " In the context of the method of treatment of the present invention, an effective amount of an agent which destabilizes lysosomes is an amount sufficient to effect beneficial or desired results, including clinical results, and, as such, an effective amount of the agent is one which provides an alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable". As evidenced by Adamson, both references teach the use of concentrations of ATRA that meet this broad definition. In response to applicant's argument that lysosomal destabilization is an attribute allegedly not sought when developing or screening drugs for anti-cancer properties, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The Applicant argues that the combination of Bard *et al.* and Yoshida *et al.* fail to teach the claimed limitations, and asserts that Yoshida *et al.* specifically teaches that "ATRA accelerates the degradation of PML-RARα in the proteasome pathway". As opposed to the instant application which is directed to the identification of agents which induce the lysosome-dependent degradative pathway, the Applicant asserts that Yoshida *et al.* therefore "teaches away" from the instant invention (Remarks, Pg. 6, Lines 11-34 and Pg. 7, Lines 1-31 and Pg. 8, Lines 1-15).

This is not found to be persuasive for the following reasons, as discussed above, the combination of references does teach the newly claimed limitations. Further, those of ordinary skill in the art would have also been aware that as lysosomes destabilize, they release lysosomal enzymes into the cytosol which would actively degrade any proteins they encounter, including the protein PML-RARα, if present. Therefore, the combined method of Bard *et al.* and Yoshida *et al.* would serve to identify an agent (retinoic acid) causing the destabilization of lysosomes in cells expressing PML-RARα and inherently increasing lysomal-dependent PML-RARα protein degradation (in addition to many other proteins). The limitation that the protein degradation be "lysosomal dependent" is inherently met as the destabilization of the lysosomes releases enzymes and would not otherwise occur, making the resulting protein degradation necessarily "lysosomal dependent".

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Paul C Martin/
Examiner, Art Unit 1653
06/08/2011

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652